REMARKS

Claims 1-3, 8-10, 18-20, and 27-30 are pending.

Claims 1-3, 8-10, 18-20, and 27-30 were all previously allowed (Office Action of 15 July 2004, and Office Communication dated 24 February 2005), however except for claim 27, which remains allowed, Claims 1-3, 8-10, 18-20, and 28-30 have now been rejected in view of a new Examiner on allegedly new grounds.

Applicants acknowledge the Examiner's objection of claim 20. Applicants have amended this claim to depend from claim 18, thereby obviating this rejection.

Applicants acknowledge the Examiner's objection to the last Sequence Listing amendments. Applicants have *traversed* this rejection, because the objection has no basis.

Applicants acknowledge the Examiner's rejection of claims 1-2, 8-9, 18-20 and 29-30, under 35 USC 112 first paragraph as allegedly lacking enablement. Applicants have *traversed* this rejection.

Applicants acknowledge the Examiner's rejection of claims 1, 3, 8, 10, 19, 28 and 29, under 35 USC 102(b) as being allegedly anticipated by Scott et al. Applicants have *traversed* this rejection.

No new matter has been added.

FORMALITIES

Supplemental IDS. While applicants are not aware of any additional art to be made of record in this application, the Examiner has not initialed the p49 for two foreign patent references (WO0161356 and WO05016966) provided in applicants' IDS of 24 August 2005 that was considered by the Examiner on 27 October 2005. Applicants, therefore, submit herewith a Supplemental IDS to re-provide these two references to the Examiner.

Telephonic Interview with Supervisory Examiner. The undersigned Applicants' agent contacted the Supervisory Examiner, Mr. Jeffrey Siew, in this case by telephone on the 08 or 09 of January 2006 to object to the present Office Action in view of the fact that all claims had previously

been allowed by the prior Examiner (who left on maternity leave), and were now being rejected on allegedly new grounds by a substituted Examiner. Mr. Siew stated that he would review the case and get back to applicants' representative. No response has ever been received from Mr. Siew, despite additional inquiries by applicants' agent. Applicants appreciate that Examiners may need to take maternity leave, but respectfully object to the inconsistent examination and non-responsiveness by the Office.

Claim Objections

Claim 20. The Examiner has objected to claim 20 because it does not further limit claim 19 from which it depends. Applicants have amended claim 20 to depend from claim 18 as suggested by the Examiner. Applicants, therefore, respectfully request withdrawal of this objection.

Sequence Listing. The Examiner has objected to amendments made to the Sequence Listing as introducing new matter into the specification, alleging that the amino acids at amended positions 31, 86, 148, 198, 282 and 303 are not consistent with amino acids at these positions in the originally filed Sequence Listing.

Applicants respectfully contend that this objection is erroneous. Applicants point out that the amino acid sequence set forth in SEQ ID NO:2 of the originally filed Sequence Listing was inadvertently numbered incorrectly, whereby all amino acid positions were off by one position—beginning at amino acid position 20, until amino acid position 340. Thus, for example, counting the Met as amino acid #1, the Ala designated in the original listing as amino acid #20 should be designated as amino acid #21. This inadvertent numbering error was subsequently corrected during prosecution, and the sequence set forth as SEQ ID NO:2 in the newly amended Sequence Listing, filed August 24, 2005, is correctly numbered. As a result, the numbering of the currently disputed amended positions is inconsistent with the numbering of those same positions in the originally filed Sequence Listing. In fact, however, the amino acids at positions 31, 86, 148, 198, 282 and 303 are actually the same between the original and amended sequence. Therefore, the amendments made to

the Sequence Listing at the designated positions are supported by the original disclosure and do not introduce new matter.

Applicants, therefore, respectfully request withdrawal of this objection.

35 U.S.C. §112, first paragraph

Claims 1-2, 8-9, 18-20 and 29-30 are rejected, under 35 U.S.C. §112, first paragraph, as having an allegedly broad scope that is not commensurate with the specification. Specifically, it is alleged that while the specification is enabling for an isolated polypeptide *consisting of* SEQ ID NO:1 or comprising SEQ ID NO:2, it does not reasonably provide enablement for any polypeptide comprising SEQ ID NO:1, having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419 or about 350-419 amino acids from SEQ ID NO:2, which bind to the extracellular domain of HER-2.

In particular, the Examiner urges that the specification teaches that p68HER-2 and ECDIIIA bind to p185HER-2, but provides no evidence that any other isolated polypeptide would so function. The Examiner points to several references that allegedly teach how single amino acid substitutions can lead to dramatic changes in biological activity. The Examiner urges that although the specification teaches that the binding affinity resides in the 79 amino acid terminal portion of p68HER-2 (*i.e.* ECDIIIa), the residues critical for this binding have not been identified. Thus, the Examiner urges that one could not predict which truncated version of the 79 amino acid portion would retain its ability to bind HER-2. Further, the Examiner prophetically argues that the claimed subject matter encompasses polypeptides that would be expected to have an altered configuration, folding or shape (*i.e.* due to truncations or additions), and that one could not predict whether such an alteration of the polypeptide would function as claimed. The Examiner concludes that in the absence of any guidance or working examples, the specification provides no evidence that one of skill in the art could predict that the subject matter functions as claimed without undue experimentation.

This rejection is respectfully *traversed* in the arguments presented here below.

Relevant Law:

To satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971) (emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

There is, therefore, no requirement for disclosure of every species within a genus. Applicants are entitled to claims that are commensurate in scope not only with what applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicants have disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, with include: the quantity of experimentation necessary, the amount of direction or guidance presented, the

presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Formann, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Wands Analysis:

As described below, a consideration of the factors enumerated in In re Wands demonstrates that the application, in conjunction with what was known to one of skill in the art as well as the other relevant factors, teaches how to make and use the full scope of the claimed subject matter. General techniques for isolating, expressing, and testing polypeptides comprising all or part of the sequence of p68HER-2 set forth in SEQ ID NO:2, including the ECDIIIa portion set forth in SEQ ID NO:1, are provided in the specification and are known to the skilled artisan, as discussed in detail below, and any necessary adjustment can be determined empirically using routine testing. Having taught the full length polypeptide and the ECDIIIa portion and demonstrated binding thereof, and having taught assays for testing polypeptides that contain portions of these polypeptides to assess activity, it would not require undue experimentation to identify polypeptides that bind to the ECD of HER-2 with an affinity binding constant of at least $10^8 M^{-1}$. It would, therefore, not require undue experimentation for one of skill in the art to make and use the claimed subject matter.

*1) **Scope of the Claims***. The claims are directed to isolated polypeptides of p68HER-2, or fragments thereof including the 79 amino acid terminal fragment of p68HER-2 termed ECDIIIa, that bind to the ECD of HER-2 with a specified binding affinity, and to pharmaceutical compositions that contain the polypeptides. Claim 1 is directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, or fragments thereof that are about 50 to 79 contiguous residues in length that binds to the ECD of HER-2. Dependent claim 2 specifies that the polypeptide is from about 69 to 79 amino acids in length. Claim 8 is directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2, or fragments thereof that are about 80 to 419 amino acids in length that contain the 79 amino acid C-terminal portions and that bind to the ECD of HER-2. Dependent claim 9 specifies that the polypeptide is from about 350 to

419 amino acids in length and contains three N-linked glycosylation sites. Claims 18-20 and 29-30 are directed to pharmaceutical compositions containing the polypeptides set forth in claims 1-2 and 8-9, respectively.

The claims are clearly within the scope of what is taught in the specification, *i.e.*, a genus of polypeptides of p68HER-2 that includes the particular claimed polypeptides. The specification teaches that p68HER-2 binds to the ECD of HER-2, and further teaches that a fragment thereof of 79 amino acids also binds to the ECD of HER-2. The specification teaches the sequence, expression, cloning, and purification of p68HER-2 and related truncated polypeptides (*i.e.* the 79 amino acid ECDIIIa peptide), and provides detailed assays for assessing their binding affinity. By following the teachings of the specification, one of skill in the art can readily make the claimed polypeptides and measure their binding affinity. Therefore, the scope of the claims is commensurate with the teachings of the specification.

*2) **Level of Skill in the Art.*** The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

*3) **Knowledge of those of Skill in the Art.*** At the time of filing of the instant application, a broad body of knowledge was available and known about HER-2 and other tyrosine kinases. Many of these articles and patents have been made of record in this application. For example, the sequence of HER-2 was known, its structural and biochemical properties determined, and its overexpression associated with a variety of carcinomas. Truncated variants containing regions of the extracellular domain (ECD) of a variety of HER family RTKs was known, many of them produced by proteolytic processing of full length receptors or by alternative processing (see *e.g.*, Lee and Maihle, (1998) Oncogene, 16:3243). For example, truncated variants of HER-2 were known and analyzed for function. Among these include a proteolytically shed product containing the extracellular domain (ECD) found in breast carcinomas, and a truncated ECD of HER-2 generated as an alternative transcript (see *e.g.*, Scott et al., (1993) Mol. Cell. Biol. 13:2247). In addition, a truncated ECD of related EGFR also was known, and characterized to exhibit ligand-

binding, and affect the function of receptor activation and signaling (see *e.g.*, Basu *et al.*, (1989) *Mol. Cell. Biol.*, 9:671).

The above references exemplify a variety of published protocols for the identification, production and/or analysis of truncated receptor tyrosine kinase products, including truncated HER-2 polypeptides, and the analysis of such peptides in binding assays and/or or other functional assays. The references show that such procedures were available at the time of filing of the application, and thus evidence the state of the art at the relevant time.

4) Teachings of the Specification and Working Examples. As discussed herein, the claims are directed to p68HER-2 polypeptides and fragments thereof that bind to the ECD of HER-2 with a binding affinity of 10^8M^{-1}. Included among these polypeptides are polypeptides or fragments of polypeptides having the sequence of amino acids set forth in SEQ ID NO:1 or SEQ ID NO:2. Hence, the "genus" encompasses the exemplified species and other species that are similar to the exemplified species because they exhibit all or part of the sequence of SEQ ID NO:1 or SEQ ID NO:2 and have binding affinity for the ECD of HER-2. The specification teaches such genus of polypeptides and teaches their sequence, cloning, expression, and purification and assays to test their binding affinity to the ECD of HER-2.

The specification teaches the detailed structural and functional characterization of a naturally occurring inhibitor of HER-2, p68HER-2. The specification describes that p68HER-2 binds to p185HER-2 and that the binding affinity of p68HER-2 resides in the novel proline rich ECDIIIa domain, rather than the N-terminal subdomains I and II of p68HER-2. The specification teaches that the proline rich ECDIIIa domain is a retained intron 8 sequence of 79 amino acids. The specification teaches how to clone, purify, and test the binding affinity of the 79 amino acid fragment of p68HER-2. The specification, and declarations of record, also teach exemplary anti-tumor assays.

The Working Examples exemplify the teachings of the specification. *Example 1* illustrates the amplification of a novel HER-2 ECD sequence from a SKOV-3 cDNA library (known to overexpress HER-2) using primers designed around exon 1 and exon 9 of HER-2. Example 1 further describes the characterization, subcloning, and sequence analysis of the unique HER-2

product and the identification of a retained intron sequence in-frame with the adjacent 5' HER-2 sequence of the extracellular domain, termed ECDIIIa. *Example 2* details the characterization of the HER-2 gene structure in the region of the ECDIIIa sequence, and illustrates that the retained ECDIIIa sequence is contiguous with HER-2 exons and is retained intron 8. *Example 3* exemplifies that ECDIIIa is the only retained intron within the coding sequence of HER-2.

Example 4 describes the cloning and expression of a His-tagged ECDIIIa peptide for the generation of an antibody against ECDIIIa, and the use of such antibody to demonstrate that a protein product is expressed containing ECDIIIa. Specifically, *Example 4* details the amplification of the fragment of p68HER-2 containing the ECDIIIa sequence by using primers complementary to the 5' or 3' end of the known ECDIIIa sequence, and the cloning of the amplified PCR product into a pET30a vector which also encodes a six histidine tag at the amino-terminus of the expressed protein. Using the resulting expression vector, termed pET-ECDIIIa, a his-tagged ECDIIIa protein was produced and injected into rabbits to yield antisera directed against the ECDIIIa peptide. *Example* 4 further details that a 68 kDa protein from the cell extract and extracellular media of SKBR-3 cells reacted with the anti-ECDIIIa antibody and with an antibody to the N-terminal sequence of p185HER-2 (*i.e.* ECD region), by immunoprecipitation followed by western blotting, indicating that p68HER-2 contained the N-terminal sequence of p185Her-2. *Example 4* also exemplifies the expression of p68HER-2 in the cell extracts and extracellular media of HEK293 cells and in a variety of carcinoma cell lines.

Example 5 exemplifies results of a ribonuclease protection assay (RPA) to assess expression of an alternative HER-2 product containing ECDIIIa sequence, using an RNA antisense probe designed to protect a 370 nucleotide fragment when hybridized with mRNA containing ECDIIIa adjacent to HER-2 exon sequence and to protect an 87 nucleotide fragment when hybridized with fully spliced HER-2 RNA. *Example 5* details the construction of the antisense RNA probe and the methodology of the RPA on various cell lines, and shows that the alternative transcript is expressed in most all cell lines tested as a small percentage of p185Her-2 mRNA. *Example 6* exemplifies the expression of the alternative HER-2 transcript in human tissue, including human embryonic kidney and liver. *Example 7* further details the expression of a protein containing the ECDIIIa sequence

using the anti-ECDIIIa antibody, and exemplifies the specificity of the antibody by using preimmune sera or blocking the reactivity of the antibody by preincubation with a purified ECDIIIa peptide. *Example 8* exemplifies a comparison of the protein expression of p68HER-2 and p185HER-2 and shows that p68HER-2 levels are markedly reduced in carcinoma cells known to overexpress HER-2.

Example 9 illustrates binding of p68HER-2 and ECDIIIa to p185HER-2. Specifically, *Example 9* exemplifies interaction of p68HER-2 and p185HER-2 following immunoprecipitation of the proteins using antibodies directed to the extracellular domain of both p68HER-2 and p185HER-2 (anti-neu (N)) or specific for the C-terminal domain of p185HER-2 only (anti-neu(C)). Western blotting of the immunoprecipated material with an anti-ECDIIIa antibody for p68HER-2 or anti-Neu(C) for p185HER-2 confirmed an interaction of the proteins by their co-immunoprecipitation. *Example 9* also describes binding of the 79 amino acid ECDIIIa to p185HER-2 in a "pull-down" assay by immobilization of the His-tagged ECDIIIa peptide to nickel agarose, followed by incubation of the immobilized peptide with protein extracts prepared from HER-2 transfected cells. After washing, the bound proteins were eluted and the product shown to be reactive with an anti-p185HER-2 antibody. *Example 9* exemplifies the specificity of the interaction using control His-tagged proteins. *Example 9* further details the assessment of the binding affinity of ECDIIIa to p185HER-2 by incubation of increasing concentrations of His-tagged ECDIIIa peptide with cells transfected with HER-2 or control parental cells. Binding was detected by Western blot using antibodies specific for ECDIIIa and binding affinity determined.

Example 10 exemplifies analysis of tyrosine phosphorylation of p185HER-2 by p68HER-2 and ECDIIIa. Cells transfected with p185HER-2 were incubated with purified ECDIIIa peptide or conditioned media containing p68HER-2 and tyrosine phosphorylation assessed by Western Blot using antibodies against phosphotyrosine. *Example 10* illustrates that p68HER-2 and ECDIIIa do not stimulate phosphorylation of p185HER-2.

Therefore, as demonstrated, the specification provides detailed knowledge and Working Examples of the characterization, cloning, purification, and function of p68HER-2, and polypeptide fragments thereof (*i.e.* 79 amino acid fragment).

5) ***Predictability.*** As is known to those of skill in the art (described above), the level of knowledge and skill in the identification, characterization, cloning, purification, and testing of alternative HER isoforms, including the p68HER-2 polypeptide and fragments thereof as claimed in the instant application, was high as of the effective filing date. Therefore, given the extensive teachings of the specification, in combination with what was known at the time the instant application was filed, it is not unpredictable that p68HER-2 and fragments thereof can be generated and tested for their ability to bind p185HER-2, and those that bind identified.

The Office Action alleges that the specification provides insufficient guidance with regard to making the broadly claimed polypeptides and that one of skill in the art would be unable to predict the claimed subject matter would function with a reasonable expectation of success. Specifically, the Examiner urges that in the absence of knowing the residues of ECDIIIa that are critical to binding, it could not be predicted which truncated version of SEQ ID NO:1 would function. In addition, the Examiner urges that the effects of truncations of SEQ ID NO:1 or SEQ ID NO:2 cannot be predicted because the truncations would be expected to alter the configuration of the polypeptide which would be expected to affect the conformation of the binding site. Similarly, the Examiner urges that a polypeptide *comprising* SEQ ID NO:1 would include unlimited amino acid residues at one or both of the N or C terminus, which also would alter the protein folding and could "mask" the sequence of SEQ ID NO:1 required for binding. In support of this, the Examiner cites a number of references that teach how single amino acid substitutions can lead to dramatic changes in biological activity (*i.e.*, Bowie *et al.*; Rudikoff *et al.*; Burgess *et al.*).

It is respectfully submitted that each of the above reasons is not relevant to the issue under consideration. The claims are directed to polypeptides of SEQ ID NO:1 or SEQ ID NO:2, or fragments thereof, that ***bind to p185HER-2 with a binding affinity of*** $10^8 M^{-1}$. This functional limitation naturally excludes polypeptides that would not bind to p185HER-2 because, for example, they no longer contain the binding site and/or the polypeptides are folded in such a way to "mask" the binding site.

Furthermore the specification teaches the entire sequence of the polypeptides, demonstrates activity of several and provides assays to assess the activity of any others. Systematically removing

residues and, if necessary, testing the resulting polypeptides for activity is routine and readily achieved. The sequence of every such polypeptide is known in view of the disclosure of the application.

Given that the specification teaches that a polypeptide of SEQ ID NO:2 of 419 amino acids, *and* a polypeptide fragment thereof of 79 amino acids set forth in SEQ ID NO:1, bind to p185HER-2, it is not unpredictable that other polypeptide fragments also bind p185HER-2. Importantly, the specification teaches that a polypeptide *comprising* SEQ ID NO:1 (*i.e.* a his-tagged ECDIIIa peptide, or p68HER-2) binds to p185HER-2. One of skill in the art could predictably make the polypeptides as claimed, such as by using standard recombinant DNA techniques to serially truncate the sequence of SEQ ID NO:1 and SEQ ID NO:2, and test the resulting polypeptides for their ability to bind p185HER-2.

Yet, the Examiner urges that the present specification does not reasonably provide enablement for any "polypeptide comprising SEQ ID NO:1, having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419 or about 350-419 amino acids from SEQ ID NO:2, which bind to the extracellular domain of HER-2." The Examiner is respectfully requested to further reconsider this rejection based on the following additional comments.

First, the claims to refer to *contiguous* residues (e.g. to "50-79 contiguous" or "69-79 contiguous" residues), which reasonable should alleviate much of the Examiner's concern.

Second, the instant teachings and examples show that p68HER-2, and the intron-encoded ECDIIIa subregion thereof, both bind with a very high affinity to HER-2. Significantly, the fact that high affinity binding is retained by the 79 amino acid ECDIIIa subregion would <u>not</u> suggest to one skilled in the art that the entire 79 amino acids are *essential* for high-affinity binding, but rather only that the minimal region sufficient for binding is contained therein. Accordingly, applicants have justifiably claimed a somewhat smaller *contiguous* region, limited, by the recited functional proviso that the region must still demonstrate high-affinity binding (at least 10^8 M^{-1}) to HER-2, the hallmark of the present invention. Thus applicants teach a region, and further teach how to rapidly identify operative embodiments. The functional binding limitation serves to assure that the scope of the

claimed subject matter is commensurate with the teachings of the specification. The scope of the claimed genus is substantially narrowed by recitation of contiguous amino acid residues.

Third, in further confirmation of the reasonable basis for claiming regions of at least 50 contiguous amino acids, several of applicants' copending applications disclose specific active polymorphic variants of Herstatin that correspond to *non-conservative* amino acid substitutions. Significantly, 6 of these non-conservative variable positions occur within the first 21 amino acid positions. This finding confirms the instant teachings and disclosure that the minimal binding region is contained in a subregion of ECDIIIA (*e.g.*, of about 50 to 79 residues).

Fourth, the instant specification teaches heterologous fusion proteins with the ECDIIIa region. Applicants have demonstrated and taught the binding properties of the full-length p68HER-2 and the ECDIIIa sub-fragment (*see* Example 9, and Figure 5). The particular ECDIIIa sub-fragment tested in Example 9 was expressed from the pET30a vector (Novagen; see specification at page 17, line 11-12) and thus represents a significant *fusion* protein of ECDIIIa (referred to herein as the His-tagged ECDIIIa fragment (ECDIIIa fragment)), comprising a heterologous amino terminal region of about 50 amino acids having: a poly-histidine tag; a thrombin cleavage site; an S-tag region; and an enterokinase site. Therefore, applicants have not only disclosed a smaller contiguous binding region, but have demonstrated its function in the context of much larger polypeptides; namely p68HER-2, and more significantly—a sizable *diverse* fusion protein. Therefore, contrary to the position urged by the Examiner, a person of ordinary skill in the art would <u>not</u> reasonably conclude that added amino acids would obscure and prevent SEQ ID NO:1 residues from mediating high-affinity binding to p185HER-2.

Thus, the teachings of the specification are widely applicable to make and use truncated fragments of SEQ ID NO:1 or SEQ ID NO:2 that exhibit binding affinity to p185HER-2. The specification provides detailed procedures and assays to generate the polypeptides and to test the binding affinity of truncated polypeptides. Therefore, it is respectfully submitted that a high degree of knowledge was available at the time of filing of the instant application, to render the instantly claimed polypeptides predictably generated and tested for binding affinity to p185HER-2.

Conclusion. In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, it would not require undue experimentation for a person of skill in the art to isolate a p68HER-2 polypeptide, or fragment thereof, and determine its binding affinity to the ECD of p185HER-2. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rebuttal to Examiner's Arguments:

First, it is noted that this rejection is listed as a "new ground" of rejection. Actually, an almost identical rejection was set forth in the Office Action dated August 01, 2001, which was obviated by the response and amendments filed 20 February 2002 as indicated by the withdrawal of the rejection in the Office Action dated May 22, 2002. Thus, the present rejection is inconsistent with previous prosecution, most likely due to the change in Examiner because the prior Examiner left for maternity leave. According to MPEP 706.04, "full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner, or make a new search in the hope of finding something."

In addition, it is respectfully submitted that analysis of enablement requires consideration of all of the "Wands Factors;" focusing on one or two is a misapplication of the law. All factors must be considered and weighed. A deficiency in meeting one factor does not preclude a finding of enablement. In the instant case, the Examiner only urges that it is not predictable what effects truncations or addition of SEQ ID NO:1 or SEQ ID NO:2 would have on the function of the polypeptides. It is noted that predictability is only one factor that should be considered. The claimed subject matter requires that the polypeptides bind to the ECD of p185HER-2 with a specified binding affinity. Given the teachings of the specification, presence of working examples,

the state of the prior art, and the relative skill of the in the art, one of ordinary skill in the art could predictably generate polypeptides as claimed.

Further, the reliance on *Rochester v. Searle* (*358 F.3d 916, Fed Dir., 2004*) is misplaced; it addresses written description not enablement, which are distinct. In addition, the facts pertinent to the findings in *Rochester v. Searle* are distinct from the instant claims. The claims at issue were claims in the Rochester '850 patent directed to screening assays for use in determining whether a particular drug selectively inhibited the activity of COX-2, which was thought to be responsible for the inflammation associated with diseases such as arthritis, without inhibiting COX-1 activity. The '850 patent did not disclose any compound that would function as claimed, nor provided any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research. Thus, the court concluded that the '850 patent lacked adequate written description; the question of enablement was considered moot and not addressed in the Federal Circuit decision.

In contrast, the instant claims are *not directed to screening assays*, but are directed to the polypeptides, which are disclosed in the application. The application provides polypeptides, including their sequence, cloning, purification, and methods for testing their binding to p185HER-2. Thus, the findings in *Rochester v Searle* are inapt with respect to the instantly claimed subject matter, and if apt, do not lead to a conclusion of lack of enablement, since the instant application provides compounds that have the requisite activity.

Public policy considerations. Applicants are entitled to claims that are commensurate in scope not only with what applicants have specifically described and exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicants have disclosed. In this instance, applicants have disclosed and taught several variants of p68HER-2, including a truncated form that contains only the intron-encoded portion (*i.e.* ECDIIIa). Applicants are the first to identify any p68HER-2 (herstatin) polypeptide, and fragments thereof, and the first to recognize that the retained intron encoded portion (ECDIIIa) alone is able to bind to the ECD of p185HER-2.

It is unfair and unduly limiting and contrary to the public policy upon which the patents laws are based to require applicants to limit the claims to the exact sequences exemplified, when the

application clearly teaches how to make and use polypeptides that vary from the exemplified polypeptides. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

If applicants are required to limit the claims as suggested by the Examiner, then those of skill in the art can, by virtue of the teachings of this application, readily prepare polypeptides that differ in a few residues, thereby practicing what is disclosed in the application, but avoiding infringing such limited claims. The instant application provides a broader disclosure; and having done so, places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims. To permit that is simply not fair. Small early stage companies can ill-afford to dedicate their innovations to the public.

Additional Rejection under 35 U.S.C. §112, first paragraph

Claims 18-20 and 29-30 are rejected, under 35 U.S.C. §112, first paragraph, as being broader than the enabling disclosure. Specifically, it is alleged that while the specification is enabling for a pharmaceutical composition for treating solid tumors that overexpress HER-2, where the composition comprises a polypeptide of SEQ ID NO:2, the specification does not reasonably provide enablement for any pharmaceutical composition containing a polypeptide whose sequence consists of SEQ ID NO:1, comprises SEQ ID NO:1, or comprises the claimed fragments of SEQ ID NO:1 or SEQ ID NO:2.

In particular, the Examiner urges that although the specification and Declarations of record exemplify the efficacy of p68HER-2 (set forth in SEQ ID NO:2), it cannot be predicted that any

other isolated polypeptide would function as claimed. The Examiner concludes that in the absence of any guidance or working examples, the specification provides no evidence that one of skill in the art could predict that the subject matter functions as claimed without undue experimentation. This rejection respectfully is traversed.

For the reasons detailed above, it is respectfully submitted that the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, it would not require undue experimentation for a person of skill in the art to make and use a pharmaceutical composition as claimed for treating solid tumors that overexpress HER-2. Insofar as p68HER-2, and polypeptide fragments thereof, are enabled, pharmaceutical compositions containing these polypeptides also are enabled.

Specifically, the specification provides explicit teaching of anti-tumor cell activity by p68HER-2 in an assay assessing anchorage independent growth of cells in soft agar, which is an art recognized and predictive procedure to examine transforming activity (see *e.g.*, page 13, lines 5-23, and Figure 7). Specifically, the specification teaches that p68HER-2 inhibits anchorage independent growth of two cells lines (SKOV-3 and 17-3-1 cells, both which overexpress HER-2). In addition, the Declarations of record of November 22, 2002 by Dr. Gail Clinton and Dr. Edward Neuwelt further demonstrate the efficacy of p68HER-2 in *in vivo* models of tumor cell activity using other art recognized assays that were known to one of skill in the art at the time of filing the instant application.

Importantly, the Declarations, and references of record therein, evidence the high level of skill in the art and knowledge of skill in the art, particularly with respect to assaying for compounds for treating solid tumors. Thus, it is respectfully submitted that a high degree of knowledge was available at the time of filing of the instant application, that in combination with the teachings of the specification, render the instantly claimed compositions predictably generated and tested for anti-tumor activity.

Furthermore, the Examiner has provided no evidence that the polypeptides cannot be formulated as a pharmaceutical compositions and so-used. The claims recite that the polypeptides

have a recited binding affinity, which the exemplified polypeptides possess. The Examiner has provided no evidence that a polypeptide that has such affinity does not possess pharmaceutical activity.

Further Rejection under 35 U.S.C. §112, first paragraph

Claims 18, 20, and 30 are rejected, under 35 U.S.C. §112, first paragraph, as not being enabled. It is noted that the reasoning for this rejection was incomplete. It seems the Examiner alleges that the Specification is not enabling for a pharmaceutical composition for treating solid tumors comprising a monoclonal antibody that binds to the extracellular domain of p185HER-2, and a polypeptide of SEQ ID NO:2 or fragment thereof.

This rejection is respectfully traversed.

Specifically, the Examiner alleges that it would be expected that the monoclonal antibody to the extracellular domain of p185HER-2 would bind to SEQ ID NO:2 and sequester it in solution. Thus, the Examiner alleges that it is not clear how the complexed antibody/SEQ ID NO:2 composition would be expected to bind to p185HER-2 *in vivo*. The Examiner urges that the specification provides no guidance or exemplification of the claimed subject matter to allow one of skill in the art to predict the subject matter would function as broadly claimed without undue experimentation.

First, it is respectfully submitted that the rejection of claim 20 is in error. Claim 20 is directed to a pharmaceutical composition that is a combination of a polypeptide of SEQ ID NO:1, or a fragment thereof, and the monoclonal antibody that binds to the ECD of HER-2. Claim 20 does not recite a polypeptide of SEQ ID NO:2. Thus, for the reasons set forth by the Examiner, there is no basis for the rejection of claim 20.

Further, it is noted that the Examiner is alleging *inoperability*, which is an issue under 35 U.S.C. §101. Based upon a lack of utility, a rejection of lack of enablement follows, since one cannot teach how to use something that allegedly has no use. No rejection under 35 U.S.C. §101 is set forth. Further, the rejection as set forth is based on unsupported conjecture.

No evidence is provided to support the Examiner's position that the "monoclonal antibody to the extracellular domain of p185Her-2 would bind to SEQ ID NO:2 and sequester it in solution," such that the monoclonal antibody and the polypeptide of SEQ ID NO:2 would be unable to bind to the ECD of p185HER-2. No reference is provided to show that a monoclonal antibody in combination with the polypeptide of SEQ ID NO:2 would inhibit the binding of SEQ ID NO:2 to the ECD of p185HER-2. The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The facts of which the Examiner is taking notice are conclusory and are not capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

Hence, if this position is maintained, the Examiner must provide a reference supporting this position.

In this instance, it is respectfully submitted that, it would not require undue experimentation for a person of skill in the art to assay for compounds as claimed for treating solid tumors. The specification teaches that p68HER-2 is effective at treating solid tumors, and further teaches assays to test for anti-tumor activity. In addition, a high degree of knowledge was available at the time of filing of the instant application to enable the use of an antibody that binds to the extracellular domain of HER-2, for treating solid tumors. In fact, the Examiner cites several references that describe the ability of various antibodies that bind the extracellular domain of HER-2 to inhibit tumor growth (see *e.g.*, Stancovski *et al.*, (1991) 88:8691; Lewis *et al.*, (1993) *Cancer Immunology Immunotherapy*, 37: 255; U.S. Patent No. 5,677,71 and others.). The references evidence the high level of skill in the art and knowledge of skill in the art, particularly with respect to assaying for compounds for treating solid tumors. Furthermore, the references are significantly earlier than the

priority date of the application; level of skill and knowledge of those of skill in the art was higher by 1999 than is evidenced by these references.

It would not require undue experimentation for one of skill in the art to combine the polypeptides provided in this application, with other compounds that also were known to one of skill in the art at the time of filing the application to inhibit tumor growth (*i.e.* antibodies to the ECD of the HER2 receptor). The instant application provides polypeptides, and those of skill in the art are aware of antibodies that possess the requisite anti-tumor activity. Administering them together is routine and the appropriate amounts of each to employ can be readily determined.

Furthermore, the specification is presumed enabled and correct. Unless the Examiner can provide evidence to the contrary, the claims are enabled.

Further Rejection under 35 U.S.C. §112, first paragraph

Claims 18, 20, and 30 are further rejected, under 35 U.S.C. §112, first paragraph, as failing to comply with the requirement for enablement. The Examiner urges that the specification is enabling for a pharmaceutical composition that contains Herceptin, but does not reasonably enable a pharmaceutical composition for treating solid tumors comprising any monoclonal antibody that binds to the extracellular domain of p185HER-2.

This rejection is respectfully traversed.

Specifically, the Examiner urges that one cannot extrapolate the teaching of the specification to the scope of the claims because implicit in the use of the pharmaceutical composition is the effective use of the composition in the treatment of solid tumors. The Examiner cites various references that allegedly show that some, but not all, antibodies to the ECD of HER2 are effective at treating solid tumors. Thus, the Examiner urges that the specification provides no guidance or exemplification of the claimed subject matter to allow one of skill in the art to predict the subject matter would function as broadly claimed without undue experimentation.

It is noted that the presence of *inoperative* embodiments does not necessarily render a claim non-enabled. The standard is whether a person of skill in the art could determine which embodiments that were conceived would be inoperative or operative with expenditure of no more

effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577-78, (Fed. Cir. 1984). If such a determination cannot be made without undue experimentation, then the claim is invalid. See Graver Tank & Mfg. Co., Inc. v. Linde Air Products Co., 336 U.S. 271, 276-77 (1949), affirmed on rehearing, 339 U.S. 605 (1950); In re Cook and Merigold, 439 F.2d 730, 732-33 (C.C.P.A. 1971).

While the Examiner has cited references to evidence that not all antibodies are effective, the papers in fact demonstrate the availability of antibodies that are effective significantly earlier than the priority date of this application, and rebuts her own rejection. The references cited by the Examiner support the instant claims and exemplify that one of skill in the art could determine which monoclonal antibodies were effective to treat solid tumors. For Example, Lewis *et al.* (*Cancer Immunology Immunotherapy*,(1993) 37: 255) tested the antiproliferative activities of six different anti-p185HER2 antibodies on a variety of different cells lines characterized for their overexpression of p185HER-2. Contrary to the interpretation by the Examiner, the results of this study show that the 4D5 antibody (Herceptin) and the 3H4 antibody, that share similar epitopes, elicit almost identical proliferative responses on each tumor cell line tested. In addition, other antibodies tested also were effective at inhibiting proliferation of tumor cells. Based on this knowledge, one of skill in the art could determine and test for an operative antibody, consistent with the scope of the claimed subject matter.

The claims are directed to p68HER-2 polypeptides and fragments thereof that bind to the ECD of HER-2 with a binding affinity of 10^8M^{-1}, in combination with a monoclonal antibody that binds to the extracellular domain (ECD) of HER-2. Included among monoclonal antibodies that bind to the ECD of HER-2 to treat solid tumors is Herceptin, which, as described in the specification, for example at page 12, is "a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD of HER-2." Hence, the "genus" encompasses the exemplified species of Herceptin, and other species that are similar to the exemplified species because they bind to the ECD of HER-2 and inhibit tumor growth. The Examiner points to numerous references that demonstrate the high level of knowledge in the art at the time of filing the instant application regarding multiple species of monoclonal antibodies that bind to the ECD of

HER-2 and were known to inhibit tumor growth. Thus, given the teachings of the specification, the scope of the claims, and the knowledge of skill in the art, it would not require undue experimentation to make and use the instantly claimed subject matter. It is respectfully requested that the instant rejection be withdrawn.

Rejection under 35 U.S.C. §102(b)

Claims 1, 3, 8, 10, 19, 28, and 29 are rejected, under 35 U.S.C. §102(b) as anticipated by Scott *et al.* (*Mol. Cell. Biol.* (1993) 13:2247-2257) because Scott *et al.* allegedly disclose a concentrate of conditioned medium from SKBR-3 cells that contains a 68 kDa polypeptide which reacts with the polyclonal antibody to the extracellular domain of p185HER-2. The Examiner urges that since the polypeptide of SEQ ID NO:2 (*i.e.* p68HER2) also is 68 kDa, the claimed polypeptide *appears* to be the same as disclosed in Scott *et al.*

This rejection is respectfully traversed.

Relevant Law:

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The Claims. Claim 1 is directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1 (ECDIIIa), or fragments thereof, that binds to the ECD of HER-2 with a specified binding affinity. Dependent claim 3 recites that the polypeptide comprises SEQ ID NO:1. Claim 8 is directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 (i.e. p68HER2), or fragments thereof, wherein the last 79 C-terminal amino acids of the polypeptide are present, and the polypeptide binds to the ECD of HER-2 with a specified binding affinity. Dependent claim 10 recites that the isolated polypeptide comprises SEQ ID NO:2. Claim 28 recites that the isolated polypeptide consists of SEQ ID NO:2.

Claim 19 is directed to a pharmaceutical composition containing an isolated polypeptide comprising an isolated polypeptide having an amino acid sequence of SEQ ID NO:1, or fragments thereof. Claim 29 is directed to a pharmaceutical composition containing an isolated polypeptide comprising an isolated polypeptide having an amino acid sequence of SEQ ID NO:1, or fragments thereof.

Scott et al. Scott *et al.* discloses a truncated HER2 protein, and cellular expression of truncated HER2 proteins. Figure 5 of Scott *et al.* shows the results of an immunoblot for truncated HER2 proteins in MKN7 cells and SKBR3 cells, both known to overexpress HER2 receptor; MCF7 cells that normally express HER2 receptor; and cells transfected with a HER2 ECD expression clone (pW597.3A, containing the first 633 amino acids of p185HER-2). Both conditioned medium (CM) from the various cell lines, and cell extracts (CE) were tested. The immunoblots were probed with polyclonal antibodies to the HER2 ECD or to the HER2 C-terminus. Figure 5 of Scott *et al.* depicts an immunoreactive band to the anti-HER ECD polyclonal antibody at 60 to 70 kDa in the *cell extracts* of MKN7 and SK-BR3 cells, but **not** in the conditioned medium. Scott *et al.* discloses that this immunoreactive band represents nonspecific (non-HER2 protein) since the band was also present at near equal intensity in an MCF7 cell extract.

Differences between the claimed subject matter and the disclosure of Scott et al. Scott *et al.* does not disclose an isolated polypeptide of 68 kDa, nor an isolated polypeptide having the sequence of amino acids set forth in SEQ ID NO:2. The 68 kDa product of Scott *et al.* is merely a band in a gel. Based on the teachings in Scott *et al.*, one of ordinary skill in the art would not

conclude that the immunoreactive band at 60 to 70 kDa is the polypeptide of the instantly rejected claims. For example, Scott *et al.* states that the band at approximately 60 to 70 kDa is **not** a HER-2-derived polypeptide, but is a nonspecific, nonHER-2 protein. In addition, Figure 3 of the instant application shows that p68HER-2 is a secreted protein and is present in the extracellular medium of transfected cells, yet the immunoblot disclosed in Scott *et al.* shows that the band at 60 to 70 kDa is ***not the result of a secreted product*** since it is present only in the cell extract, but **not** the conditioned medium of the cells tested.

It is noted that the rejection of claims 19 and 29 by the Examiner was predicated on the fact that a concentration of conditioned medium could be considered as comprising a pharmaceutically acceptable carrier. Without arguing the propriety of such an assertion, it is respectfully submitted that the immunoreactive band of 60 to 70 kDa disclosed by Scott *et al.* was not present in the conditioned medium of the cells tested, but rather was present only in the cell extracts. The Examiner has provided no evidence that a cell extract is a pharmaceutically acceptable carrier. A cell extract clearly does not constitute a pharmaceutically acceptable carrier.

Thus, Scott *et al.* does not disclose every element of the rejected claims. Because Scott *et al.* does not disclose every element of the rejected claims, Scott *et al.* does not anticipate the claims. Applicants respectfully request that the rejection be reconsidered and withdrawn.

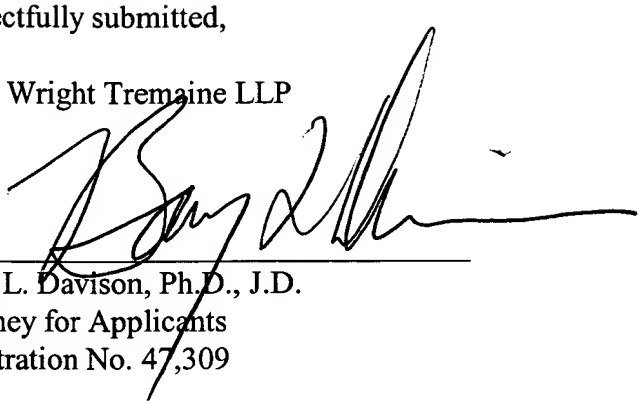
CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request entry of the present Response and Amendment, and a Notice of Allowance relating to all pending claims, all having been previously allowed.

The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite issuance of a final Notice of Allowance.

Respectfully submitted,

Davis Wright Tremaine LLP



Barry L. Davison, Ph.D., J.D.
Attorney for Applicants
Registration No. 47,309

Davis Wright Tremaine LLP
2600 Century Square
1501 Fourth Avenue
Seattle, Washington 98101-1688
Telephone: 206-628-7621
Facsimile: 206-628-7699